UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,250	09/19/2005	Roberto Tonani	17758 (PC27531A)	6204

7590 09/12/2008

Peter I Bernstein
Scully Scott Murphy & Presser
Suite 300
400 Garden City Plaza
Garden City, NY 11530

EXAMINER	
BIANCHI, KRISTIN A	
ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
09/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,250	TONANI ET AL.	
	Examiner	Art Unit	
	KRISTIN BIANCHI	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/25/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15-18* is/are allowed.

6)☒ Claim(s) *1-3,6 and 8-13* is/are rejected.

7)☒ Claim(s) *4,5 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/07/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 and 8-18 are currently pending in the instant application. Claims 1-3, 6 and 8-13 are rejected. Claims 4, 5 and 14 are objected. Claims 15-18 appear allowable.

Response to Amendment and Arguments

Applicants' arguments and amendments filed on June 25, 2008 have been fully considered and entered into the application.

Applicants' amendment to the claims has overcome the 35 USC 102(b) rejections of claims 1 and 6, the 35 USC 112 2nd rejections of claims 4 and 16, the 35 USC 112/101 rejection of claims 7 and 13, and the objection to claim 14.

In regards to the 102(e) rejection of claims 1-3 and 6, Applicants argue that the general formula (I) disclosed in Tonani et al. has a structure of Thieno [3,2-c] pyrazole whereas the instant claims are directed toward compounds with a structure of Thieno [2,3-c] pyrazole. Therefore, since the general formula (I) of the present application has a structure of Thieno [2,3-c] pyrazole, Tonani et al. does not anticipate the present application. This argument has been found persuasive and the 35 USC 102(e) rejection of claims 1-3 and 6 has been withdrawn.

In regards to the provisional nonstatutory obviousness-type double patenting rejection of claims 1-3 and 6, while Applicants have stated that the double patenting rejection will be addressed when the '360 application (11/050,360) is either issued or abandoned, it is noted that the provisional rejection is considered proper, therefore, it is maintained.

In regards to the 112 1st paragraph rejection, Applicants argue that the instant specification provides sufficient description to meet the enablement requirement. This argument is not found to be persuasive.

Applicants claim the treatment of various cancers. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancer have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al., page 531). Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

Applicants are claiming the treatment of viral infections (i.e. HIV infection or AIDS). As such, the specification fails to enable the skilled artisan to use the compounds of the formula (I) to treat HIV. In addition, there is no proof that the claimed

compounds have ever been administered to a human. The obstacles to therapeutic approaches and vaccine development with regard to retroviruses associated with AIDS in humans are well documented in the literature. See, for example, Huff {J. Med. Chem. 34(8) 1991, p. 2305-2314} on page 2314. These obstacles include and are not limited to: 1) the extensive genomic diversity associated with HIV, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a convert form, as well as via free virus transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus to traverse the blood brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face. In addition, there is no established correlation between *in vitro* activity and accomplishing treatment or prevention of viral infections, especially HIV infections, *in vivo*, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the art would not be able to use the compounds of the formula (I) since there is no description of an actual method wherein a viral infection in a host is treated.

Applicants are claiming a method which includes the treatment of neurodegenerative disorders (i.e. Alzheimer's disease). It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early

stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html).

Futhermore, Layzer et al. (Cecil Textbook of Medicine, page 2050) states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations". Alzheimer's disease has traditionally been very difficult or impossible to prevent or event o treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease" (pg. 1994).

Since the claims are drawn to a method of treating diseases caused by and/or associated with an altered protein kinase activity, it is important to point out that that "there may be 2,000 protein kinases" (Cohen et al., The development and therapeutic potential of protein kinase inhibitors, page 459) and that "nearly all protein kinases belong to the same superfamily and it seemed unlikely that small cell-permeant molecules could be developed that would inhibit one kinase specifically without inhibition at least a few others" (Cohen et al., same paragraph). Therefore, there may be various possible adverse effects when a compound of formula (I) is given to a patient to treat any of the aforementioned diseases. Much experimentation and *in vivo* testing

must be carried out to make sure that the administration of the compounds of formula (I) results in enhanced therapeutic effects without harmful side effects.

Hence, in the absence of showing of correlation between all the diseases claimed as capable of treatment with inhibition of altered protein kinase activity, one of skill in the art is unable to fully predict possible results from the administration of the compounds of formula (I) due to the unpredictability of the role of the instantly claimed compounds. For example, since it is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy.

Applicants argue that the specification provides detailed description of a variety of biology assay tests on the compounds claimed in the present invention. This is not found to be persuasive.

Receptor activity is generally unpredictable and a highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art to extrapolate to the other compounds of the claims. Also, the disclosure does not provide how this *in vitro* data correlates to the treatment of the assorted diseases claimed. The instant specification is short of any examples or data in regards to the supposed treating of the aforementioned diseases. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds.

Finally, Applicant has provided biological data to show the biological activity of the claimed compounds (i.e. Auror-2 inhibition and the resulting cell antiproliferation). Applicants do not disclose which specific cell proliferative disorders (i.e. benign prostate hyperplasia) are being targeted by the *in vitro* tests and these test results do not mention or give data for the various other unrelated disorders (i.e. cancer) which are claimed to be treated. There is no compound, let alone an entire class of compounds that can treat the various and divergent diseases claimed.

This rejection is still deemed proper and is maintained.

Maintained Claim Rejections - Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and **6** are provisionally rejected over copending Application No. 11/050,360.

- Copending Application No. 11/050,360: **Claims 1-3** and **6** are anticipated by at least compound no. 1 of **Claim 19** of the '360 Application.

Maintained Claim Rejections - 35 USC § 112

The newly amended Claim 13 now falls under the same 112 1st paragraph rejection that was made in the office action dated November 21, 2007. Several new references were disclosed in the Response to Amendment and Arguments section of this office action and they pertain to the following previously made rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-12 and amended claim 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain

subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Therefore, the Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

In re Wands, 8 USPQ2d 1400 (1988), discusses the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1. The nature of the invention;
2. The state of the prior art;
3. The predictability or lack thereof in the art;
4. The amount of direction or guidance present;
5. The presence or absence of working examples;
6. The breadth of the claims;
7. The quantity of experimentation needed; and
8. The level of skill in the art

The nature of the invention

Claims 8 and 13 are drawn to methods of treating every disease caused by and/or associated with an altered protein kinase activity. Claims 9-12 narrow the scope of Claim 8 by specifying certain disease associated with or caused by altered protein kinase activity.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacology, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instantly claimed invention is unpredictable in terms of the subject matter of **Claims 8-12 and amended Claim 13**.

As stated, pharmacology is an unpredictable art, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly complex, and one skilled in the art may recognize the claimed compounds as capable of inhibiting certain protein kinases (either directly or peripherally within the mechanism of action) in assays. However, such properties do not mean that the same group of compounds and compositions may treat the diseases in **Claims 8-12 and amended Claim 13**.

The state of the prior art acknowledges the use of certain protein kinase inhibitors in the clinic or in clinical trials. (Noble, et al. Science, Mar. 19, 2004, vol. 303, pp. 1800-5). However, there is no literature supporting the notion that Applicant's claimed compounds or any protein kinase inhibitors are capable of treating each and every of the diseases listed in Claims 8-12.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance presented which substantiates Applicant's claimed compounds as capable of treating the diseases/disorders listed in **Claims 8-12 and amended Claim 13**. The direction or guidance present in Applicant's Specification provides evidence that establishes the claimed compounds as capable of inhibiting certain protein kinases *in vitro*. No correlative *in vivo* data has been provided to support the scope of the instant claims.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims **8-12 and amended claim 13** encompass the treatment of every disease associated with or caused by altered protein kinase activity. In order to treat a disease, one would need to demonstrate what the subject population is, what the necessary dose is for efficacy, and that the subject has recovered from such a disease. Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success.

New Objections

Claims 4, 5 and 14 are objected to for depending on a rejected base claim.

Conclusion

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIN BIANCHI whose telephone number is (571)270-5232. The examiner can normally be reached on Mon-Fri 7am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kamal A Saeed, Ph.D./
Primary Examiner, Art Unit 1626

Kristin Bianchi
Examiner
Art Unit 1626

***